## REMARKS

Applicants wish to thank the Examiner for the telephonic interview conducted September 3, 2003, during which the written description and indefiniteness rejections relating to the % homology and BLAST analysis language were discussed. Also discussed was the question of whether the 5'OT-EST gene correlates with the modulation of obesity, during which discussion Applicants pointed out the specification's description of the differences between the hGH phenotype and the mutant 5'OT-EST phenotype. The Examiner agreed to consider the amendments and arguments presented herein.

Claims 8-16, 28 and 30-35 are currently pending in the application. Claim 35 is withdrawn by the Examiner as being drawn to a non-elected invention. Claims 8-10, 16, 28, 33 and 34 are amended. Claims 30 and 32 are cancelled without prejudice. Claims 33 and 34 are amended only to correct the dependency following cancellation of claim 30 from which they were formerly multiply dependent. New claim 36 is added. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Sequence Listing

Please replace the existing Paper Copy and Computer Readable Copy of the Sequence Listing with the enclosed Paper Copy and Computer Readable Copy of the Sequence Listing. As required under 37 C.F.R. §1.821(f) and (g), Applicants hereby state that the sequence listing information recorded in computer-readable form is identical to that in the paper copy of the sequence listing, and that the sequence listing introduces no new matter. The species of SEQ ID NO: 3 and SEQ ID NO: 4 has been amended to be *human*. Support for the amendment is found in the specification at, for example, page 47, lines 34 through 35.

Also, it was noted that the 123 nucleotide nucleic acid sequence shown on page 19, lines 24-26 is referenced by "see SEQ ID NO: 7," but that SEQ ID NO: 7 is 2852 nucleotides in length. This 123 nucleotide sequence is represented in the Sequence Listing (original and the corrected version filed herewith) by SEQ ID NO: 31. It is noted that the 123 nucleotide sequence of SEQ ID NO: 31 is a sub-sequence comprised by SEQ ID NO: 7. However, for the sake of clarity and thoroughness, the specification has been amended at page 19 to also state "(SEQ ID NO: 31; see SEQ ID NO: 7)." The amendment adds no new matter.

The Office Action stated that "Figure 6 contains multiple sequences which are not identified in the figure or the short description of the figure," and that "identifying the sequences with the appropriate SEQ ID NO in the figure or description of the figure would obviate the basis of the objection. Applicants submit that the amendment to the specification directed herein above adds SEQ ID NO references to the description of Figure 6, thereby obviating this ground of objection.

Information Disclosure Statement

The Office Action notes that all references listed in the specification ore not listed in the IDS filed July 18, 2000 and cautions that the listing of references in the specification is not a proper information disclosure statement. The Office Action points out, for example, that the Altschul et al. (1994) reference is not listed on the IDS.

Applicants wish to thank the Examiner for the caution. However, Applicants submit that the IDS filed July 18, 2000 disclosed those known references that may be material to the patentability of the claimed invention. The Altschul reference, for example, relates to computer algorithms of multiple sequence alignment generally and is not believed to be material to the novelty or non-obviousness of the claimed invention. This is even more clear because the claims as amended do not refer to sequence alignment.

Claim Objections

Claim 32 is objected to under 37 C.F.R. 1.75(c) as being of improper dependent form for failing to further limit the subject matter of the previous claim. Applicants submit that the cancellation of claim 32 herein is sufficient to obviate this ground of objection. Applicants also submit that because, as stated by the Office Action, claim 32 does not further limit the subject matter of the previous claim, the cancellation of claim 32 cannot be construed as surrendering any claim scope nor any scope of equivalents thereof.

Rejections under 35 U.S.C. §112, First Paragraph:

Claim 28

Claim 28 is rejected under 35 U.S.C. §112, First Paragraph for new matter with regard to the limitation "of 150 nucleotides or less" added in the previous amendment. The Office Action states that "literal support for this amendment can not be found" in the specification. The Office Action further states that "support for a probe which is preferably 5 to 150 nucleotides is found on page 15, second to last paragraph," but that "this length is not specifically associated with probe to detect mutations or polymorphisms which predispose an individual to obesity rather it is only associated with sequences which are related to fragments which encode a polypeptide hereinbefore defined in the specification." The Office Action also rejects claim 28 on the grounds of lack of enablement as a result of the alleged lack of support for the cited language. Applicants respectfully disagree.

Applicants submit that the amendment to claim 28 proposed herein to recite "detectably labeled probe of 5 to 150 nucleotides [or less]" is sufficient to overcome this ground of rejection. The language of the amendment is supported at page 15, lines 30-32. Applicants respectfully disagree with the Office Action's characterization of the language cited in support of the range as "only associated with sequences which are related to fragments which encode a polypeptide hereinbefore defined in the specification." The cited passage states:

> "Fragments of the nucleic acid sequence of a few nucleotides in length, preferably 5 to 150 nucleotides in length, *are especially useful as probes*."

The text immediately preceding this passage states:

> "The invention moreover provides nucleic acids encoding 5'OT-EST, comprising the gene *5'OT-EST* ***or variants thereof as defined herein. The nucleic acids of the invention, whether used as probes or otherwise***, are preferably substantially homologous to the sequence of *5'OT-EST* as shown in SEQ ID NOs 1, 3 and/or 5. The terms 'substantially' and 'homologous' are used as hereinbefore defined with reference to the 5'OT-EST polypeptide.

> Preferably, nucleic acids according to the invention are fragments of the 5'OT-EST sequence, or derivatives thereof as hereinbefore defined in relation to the polypeptides." (Page 15, lines 24-30; emphasis added)

In view of this text, Applicants submit that the "5 to 150 nucleotides" limitation is fully supported by the specification, which clearly states that nucleic acids of the invention, *including variants*, can be used as *probes*, and that probes are preferably 5-150 nucleotides in length. Given this description, one of skill in the art would know that the use of a variant sequence of 5 to 150 nucleotides as a probe would permit the detection of the variant, e.g., a mutation, polymorphism or other change. One of skill in the art would also know that even the wild-type form of 5'OT-EST can be used to detect or identify mutants or polymorphic forms. Thus, the claim as amended herein does not include new matter, the claim is supported by adequate written description, and the claim is enabled, both generally and with specific regard to the amended language. Applicants respectfully request the withdrawal of this rejection under §112, first paragraph.

Applicants have also added new claim 36, dependent from claim 28, that recites the limitation that "said at least one detectably labeled nucleic acid probe is 10 to 50 nucleotides in length." Applicants submit that the language of this new claim is supported in the specification at page 17, line 31 to page 18, line 3.

Claims 8-16, 28 and 30-34

Claims 8-16, 28 and 30-34 are rejected under 35 U.S.C. §112, first paragraph for lack of written description. The Office Action states that "the specification fails to adequately describe a nucleic acid encoding a 5'OT-EST polypeptide which is 90% homologous to the polypeptide set forth in SEQ ID NO: 2, 4-7, 16 or 17 and the polynucleotide set forth in SEQ ID NO: 1, 3 or 31." The Office Action also states that the "specification does not define any specific or critical features of a 5'OT-EST polypeptide sequence wherein the artisan would be able to distinguish whether a sequence would be considered a 5'OT-EST," and that "simply providing a percent homology to a particular SEQ ID NO fails to adequately describe any relevant identifying characteristics of a 5'OT-EST wherein the artisan sufficiently would recognize that the inventor had possession of the invention as broadly claimed." Applicants respectfully disagree.

According to the Written Description Guidelines, Written Description can be satisfied by complete or partial structure, physical and/or chemical properties, functional characteristics, a correlation between structure and function, the method of making the claimed invention, or combinations of these.

Applicants have amended clause (b) of claim 8 to recite the limitations 1) that the amino acid sequence encoded by the claimed nucleic acid "hybridizes under stringent hybridization conditions to any one of SEQ ID NOs 1, 3, 5 or 7, or to the complement thereof," and 2) that the "encoded amino acid sequence modulates the obesity of an animal." Support for the amendment regarding hybridization is provided at page 15, last paragraph and at page 16, in the first two paragraphs. Support for the amendment regarding modulation of the obesity of an animal is discussed below (it is to be understood that the term "modulates" is intended to encompass both an increase and a decrease in obesity). Applicants submit that the amendments set forth both the structural and functional requirements of the sequences falling within the claims. That is, the claimed nucleic acid will encode an amino acid sequence comprising one of SEQ ID NOs 2, 4 or 6 (providing *structure* defined by sequence). Alternatively, as recited in clause (b), the nucleic acid sequence will hybridize under stringent hybridization conditions to any one of SEQ ID NOs 1, 3, 5 or 7, or to the complement thereof, and the amino acid sequence encoded by such sequence will modulate the obesity of an animal. Clause (b) thus provides *structure*, in terms of structure necessary to hybridize to a given sequence, *function*, in terms of the actual hybridization, and *additional function*, in that the polypeptide encoded by such nucleic acid sequence must modulate the obesity of an animal.

Applicants submit that the specification provides the necessary written description support for the claims as amended. Not only does the specification provide details of "stringent hybridization" conditions, the specification also provides description of sequences (e.g., SEQ ID NOs: 1, 3, 5, 7, and 31 (which corresponds to *5'OT-EST-xdel*)) that satisfy the claim language requirements of hybridization and modulation of obesity. Independent claims 16 and 28 have also been amended to include the same structural and functional limitations regarding hybridization and the requirement that the encoded polypeptide modulates obesity in an animal.

With regard to the claim limitation added herein that the claimed sequences encode an amino acid or polypeptide sequence that "modulates the obesity of an animal," the Office Action expressed doubt as to the functional correlation between the 5'OT-EST gene and the modulation of obesity. The Office Action states:

> "Applicants' arguments indicate that there is a structure function relationship between the 5'OT sequence causing a modulation in weight, however, the evidence of record suggests otherwise. Given the data comparing J17 and J45 (sic) transgenic lines, one could at most conclude that expression levels, not any variation of the sequence itself (of the 5'OT-EST) may affect weight gain. *However, as indicated in the specification, the weight gain seen in the transgenic rat is more consistent with the expression of hGH which is also present on the construct used and which has been previously described in the prior art.*" (Emphasis added)

In essence, the Office Action appears to be questioning the objective truth of the teachings of the specification with regard to the role 5'OT-EST or mutants of it play in the modulation of obesity. The Examiner appears to base this conclusion on the teachings in the specification regarding references reporting the effects of hGH transgenes in animal models. Applicants respectfully submit that this is not correct.

First, the assumption that the entire effect is due to the hGH reporter is not correct, as pointed out on page 53-54 of the specification, which states:

> "Male specificity, infertility, extremely late onset obesity, a highly selective visceral accumulation of fat, but relatively normal metabolic profile, without insulin resistance, hyperphagia or hyperglycaemia distinguishes the dominant phenotype of the SLOB rats from all other known models of obesity in the rat, *including those with low endogenous rat GH expression or hGH expression from other transgenes.*" (page 53, line 38 to page 54, line 4; emphasis added)

That is, contrary to the assertion in the Office Action, the specification clearly teaches that on the basis of extensive data (including those data presented in the Examples), the dominant obesity phenotype displayed by transgenic animals expressing mutant 5'OT-EST *does not* correlate with the known effects of exogenous hGH expression. Because the mutant phenotype does not correlate with the phenotype expected for hGH transgenics, Applicants submit that the phenotype does correlate with the structure of the 5'OT-EST sequence. While Applicants believe that this description within the specification provides the proof necessary to support the

correlation between 5'OT-EST and the modulation of obesity, if the Examiner feels that this is not sufficiently persuasive, Applicants offer to provide an inventor Declaration providing further detail on this point.

In view of the above, Applicants submit that the specification provides the necessary correlation between the structure of 5'OT-EST and the functional modulation of obesity. More specifically, the specification teaches that a mutant 5'OT-EST gene expressed as a transgene modulates obesity with a pattern distinct from that caused by other known modulators (including transgenes) of obesity. Further, the fact that the *mutant* form of 5'OT-EST modulates the obesity of an animal directly implicates the wild-type form of the gene in the regulation of weight. That is, when the change in the function of the gene results in obesity, the wild-type gene must also be involved in maintaining normal weight or lack of obesity. Thus, the wild-type gene also modulates obesity.

Given the description of the structural/functional limitations requiring hybridization to a given set of described sequences and the description of the correlation between the recited structure and the modulation of obesity in an animal, Applicants submit that the claims as amended are supported by adequate Written Description. Applicants respectfully request the withdrawal of the written description rejection of claims 8-16, 28 and 30-34.

Rejections under 35 U.S.C. §112, Second Paragraph:

Claims 8-16, 28 and 30-34 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claims 8, 9, 10, 16 and 28 are said to be indefinite in the recitation of "at least 90% homologous... as determined by BLAST analysis using default parameters." Applicants submit that the amendment of each of these claims to remove reference to homology and BLAST analysis is sufficient to overcome this ground of rejection.

Claim 9 is rejected under §112, second paragraph as unclear for recitation of "a nucleic acid of claim 8, having sequences selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 16 or 17" and limitations of sequences which hybridize because SEQ ID NOs 5, 7, 16 and 17 are polypeptide sequences, not nucleic acid sequences. Applicants respectfully disagree.

With respect to this rejection and the subsequent §112, second paragraph rejections of claim 28, it is apparent that the sequence listing with which the Examiner is working with is incorrect. A copy of the Sequence Listing filed May 2, 2001 is submitted herewith for the Examiner's reference. Applicants submit that each of SEQ ID NOs 5, 7, 16 and 17 are nucleic acid sequences. Applicants note that the numbering of sequences in the Sequence Listing filed herewith is the same with respect to these sequences as in the sequence listing filed on May 2, 2001.

Claim 30 is rejected as unclear because SEQ ID NO: 16 does not set forth exons w, x, y or z and is only the polypeptide sequence Pro Leu Trp Ile. Again, SEQ ID NO: 16 is not the peptide sequence Pro Leu Trp Ile, but a nucleotide sequence of 3264 nucleotides. Applicants submit, however, that the cancellation of claim 30 herein renders this rejection moot.

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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Name: Kathleen Williams
Registration No.: 34380
Customer No.: 29933
Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel. (617) 239-0100